

CHANGES IN MITOTIC ACTIVITY OF THE UTERINE
EPITHELIUM IN MICE PRODUCED BY SMALL
DOSES OF DIENESTROL

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On the 30th day after castration of female mice atrophy of the epithelium lining the uterine cavity and of the uterine glands is more marked than on the 11th day. Injection of dienestrol in various doses into castrated mice enabled optimal doses as regards stimulation of mitotic activity of the epithelium to be determined. For the epithelium of the uterine cavity this dose was 1 μg (injected on the 11th day and 30th days), while for the epithelium of the uterine glands the dose was 0.05 μg (injected on the 11th day) and 0.01 μg (injected on the 30th day).

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From published data concerning changes in the mitotic index (MI) under the influence of estrogens [1, 2, 5-7] it is impossible to estimate the importance of the time elapsing after castration until injection of the estrogen for the changes in this index as well as optimal doses of estrogen for the uterine epithelium. The present investigation was carried out to study these problems.

EXPERIMENTAL METHOD

Experiments were carried out on female noninbred albino mice weighing 20-25 g. Two series of experiments were performed on 80 animals. Series I included 7 experimental groups (5 animals in each) of ovariectomized mice. On the 11th day after castration they received a single injection of dienestrol in a dose of 0.001, 0.01, 0.05, 0.1, 0.5, 1.0, and 2.0 μg . Control animals (6 mice) received no dienestrol. The experimental mice were sacrificed 24 h after injection of dienestrol at 11 a.m. (at the same time as the controls).

Series II consisted of five experimental groups of ovariectomized animals. On the 30th day after castration they were injected with dienestrol in a dose of 0.01, 0.05, 0.1, 1.0, and 2.0 μg . These mice also were sacrificed 24 h later, at the same time as the controls.

The uteruses were quickly removed and fixed by Navashin's method, and paraffin sections 7 μ in thickness were stained with iron hematoxylin by Gurvich's method. The values of MI were calculated separately for the epithelium lining the uterine cavity and the epithelium of the uterine glands. Mitoses in the region of the necks of the uterine glands were counted together with mitoses in the epithelium of the uterine cavities.

EXPERIMENTAL RESULTS

The state of the epithelium taken from the control mice on the 11th day after castration differed from that on the 30th day (Fig. 1a, b). On the 30th day, the epithelial surface was completely smooth, the glands were smaller and less convoluted, and the epithelium was low. On the 11th day the relief was more complex. MI for the epithelium of the uterine glands of the castrated animals in the experiments of series I was 3% and in series II 1.6%, while the values of MI for the epithelium of the uterine cavity were 1.8 and 0.48% respectively.

In the experiments of series I MI was significantly increased in the epithelium of the uterine cavity after injection of 0.05 μg dienestrol ($P=0.0001$), reaching 12.86%. When the dose was increased to 2 μg ,

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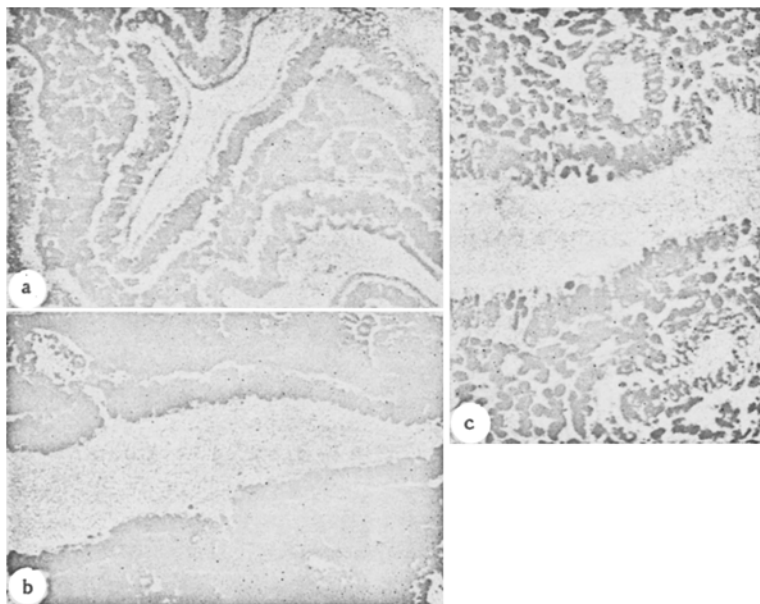


Fig. 1. Epithelium lining uterine cavity and epithelium of uterine gland. a) On 11th day after castration; b) on 30th day; c) after injection of 1 μ g dienestrol on 11th day after castration. Magnification: objective 60 \times , ocular 10 \times .

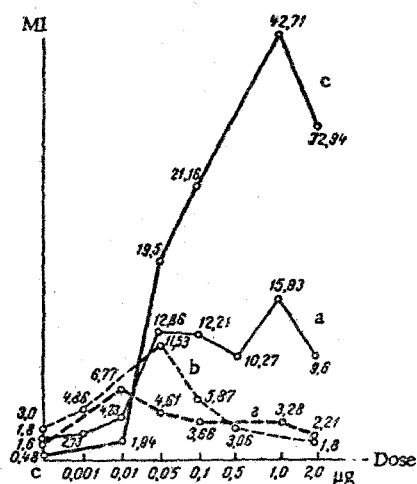


Fig. 2. Changes in MI after a single injection of dienestrol on 11th day after castration: a) epithelium of uterine cavity; b) epithelium of uterine glands; and on 30th day after castration; c) epithelium of uterine cavity; d) epithelium of uterine glands.

fluctuations in the value of MI were not significant. The epithelium of the uterine glands was more sensitive to dienestrol, and the greatest increase was observed after injection of 0.05 μ g of the preparation. Starting with a dose of 0.1 μ g (5.87%), the curve began to fall and reached a level of 1.80%, when 2 μ g dienestrol was injected, indicating inhibition of mitotic activity (Fig. 2).

In the experiments of series II, injection of 0.05 μ g dienestrol produced a sharp and significant increase (up to 19.52%) in MI in the epithelium of the uterine cavity. The increase reached maximum (42.71%) for a dose of 1.0 μ g. When 2 μ g dienestrol was injected no significant decrease was observed.

In the epithelium of the uterine glands the increase in MI reached a maximum (6.77%) after injection of 0.01 μ g dienestrol ($P = 0.013$). An increase in the dose led to a steady fall of the curve to 2.21% ($P = 0.009$) after injection of 2 μ g dienestrol (Fig. 2).

Mitoses in the epithelium of the uterine cavity were not strictly localized. However, after injection of 1 μ g dienestrol, clusters of mitoses were observed, with 5-7 mitoses in a cluster (Fig. 1c).

It can be postulated from the existence of clusters of mitoses that cells responding by mitotic division to injection of these doses of dienestrol apparently form foci in which increased proliferation of the epithelium begins, leading to increased complexity of the relief (formation of folds and crypts). Death of the epithelial cells after castration of the animal likewise took place in

zones or foci. After castration, the surrounding epithelium may be considered to be drawn toward the site of destruction of individual areas [8] on account of straightening of the folds and restoration of the smooth relief of the cavity characteristic of the uterus of castrated mice and also of mice in a certain stage of the estrus cycle (3rd day of estrus and 3rd day of diestrus).

The sensitivity of the uterine epithelium to dienestrol thus differs: the epithelium of the uterine glands is more sensitive than that of the uterine cavity [3, 4].

The fall in the MI curve may be considered to reflect a decrease in the number of cells capable of responding by mitoses to increasing doses of estrogen, and it indicates that most of them (the more sensitive) are already in a state of inhibition as a result of the action of large doses of estrogen.

Probably a similar process takes place during physiological regeneration of the epithelium during the section cycle under the influence of changes in blood estrogen levels, accompanied by a rise and fall of MI [3, 4].

The value of MI for the uterine epithelium in ovariectomized mice evidently varies slightly depending on the time elapsing after castration and before injection of dienestrol. This applies both to the epithelium of the uterine cavity (in the experiments of series I 1.80% , and in series II 0.48%) and to the epithelium of the uterine glands (3.0 and 1.60% , respectively).

Irrespective of the time after castration, the uterine epithelium remains capable of responding to the action of estrogen. In our experiment the optimal dose of dienestrol for the epithelium of the uterine cavity was $1\text{ }\mu\text{g}$ and for the epithelium of the uterine glands 0.05 and $0.01\text{ }\mu\text{g}$ (in the experiments of series I and II respectively).

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